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Document Number 4

Entry 4 of 4 File: DWPI Jul 27, 1998

DERWENT-ACC-NO: 1994-183421
DERWENT-WEEK: 200003

TITLE: New peptide(s) based on Body Protecting Cpd. - used to protect organisms against stress and disease by normalising organic functions

INVENTOR: DUVNJAK, M; GRABAREVIC, Z ; MILDNER, B ; MISE, S ; PETEK, M ; ROTKVIC, I ; SEIWERTH, S ; SIKIRIC, P ; SUCHANEK, E ; TURKOVIC, B ; UDOVICIC, I ; SIKIRICH, P ; ZAJVERT, S

PATENT-ASSIGNEE: ; DUVNJAK M[; DUVNI], GRABAREVIC Z[GRABI], MILDNER BC Z[MILDI], MISE SR BC Z[MISEI], PETEK M BC Z[PETEI], ROTKVIC IC Z[ROTKI], SEIWERTH S Z[SEIWI], , SIKIRIC PS Z[SIKII], SUCHANEK E Z[SUCHI]

PRIORITY-DATA:

1992HR-0001283	November 16, 1992
1992EP-0109145	May 30, 1992

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
RU 2116311 C1	July 27, 1998	N/A	000	C07K007/06
WO 9411394 A2	May 26, 1994	E	039	C07K007/06
AU 9456249 A	June 8, 1994	N/A	000	C07K007/06
EP 624164 A1	November 17, 1994	E	000	C07K007/06
SK 9400857 A3	January 5, 1995	N/A	000	A61K037/02
CZ 9401622 A3	February 15, 1995	N/A	000	C07K007/06
WO 9411394 A3	September 15, 1994	N/A	000	C07K007/06
HU 67982 T	May 29, 1995	N/A	000	C07K007/06
JP 07507568 W	August 24, 1995	N/A	012	C07K007/06
AU 9539142 A	February 15, 1996	N/A	000	C07K007/08
AU 678917 B	June 12, 1997	N/A	000	C07K007/08
AU 9736885 A	December 11, 1997	N/A	000	C07K007/06
EP 624164 B1	February 11, 1998	E	020	A61K038/10
DE 69316974 E	March 19, 1998	N/A	000	A61K038/10
ES 2114170 T3	May 16, 1998	N/A	000	A61K038/10
SK 279227 B6	August 5, 1998	N/A	000	C07K007/06
JP 2812803 B2	October 22, 1998	N/A	017	A61K038/00
CZ 285155 B6	May 12, 1999	N/A	000	A61K038/08

DESIGNATED-STATES: AU BG CA CZ HU JP PL RO RU SK UA US AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE AT BE CH DE ES FR GB GR IT LI NL PT SE AT BE CH DE ES FR GB GR IT LI NL PT SE

CITED-DOCUMENTS:No-SR.Pub; EP 432400 ; EP 572688

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-NO
RU 2116311C1	November 16, 1993	1994RU-0037232	N/A
WO 9411394A2	November 16, 1993	1993WO-EP03217	N/A
AU 9456249A	November 16, 1993	1994AU-0056249	N/A
AU 9456249A	N/A	WO 9411394	Based on
EP 624164A1	November 16, 1993	1993WO-EP03217	N/A
EP 624164A1	November 16, 1993	1994EP-0901809	N/A
EP 624164A1	N/A	WO 9411394	Based on
SK 9400857A3	November 16, 1993	1993WO-EP03217	N/A
SK 9400857A3	July 15, 1994	1994SK-0000857	N/A
CZ 9401622A3	November 16, 1993	1994CZ-0001622	N/A
WO 9411394A3	November 16, 1993	1993WO-EP03217	N/A
HU 67982T	November 16, 1993	1993WO-EP03217	N/A
HU 67982T	November 16, 1993	1994HU-0001952	N/A
HU 67982T	N/A	WO 9411394	Based on
JP 07507568W	November 16, 1993	1993WO-EP03217	N/A
JP 07507568W	November 16, 1993	1994JP-0511727	N/A
JP 07507568W	N/A	WO 9411394	Based on
AU 9539142A	May 28, 1993	1993AU-0043196	Div ex
AU 9539142A	November 16, 1993	1994AU-0056249	Div ex
AU 9539142A	November 29, 1995	1995AU-0039142	N/A
AU 678917B	May 28, 1993	1993AU-0043196	Div ex
AU 678917B	November 16, 1993	1994AU-0056249	Div ex
AU 678917B	November 29, 1995	1995AU-0039142	N/A
AU 678917B	N/A	AU 9539142	Previous Publ.
AU 9736885A	November 29, 1995	1995AU-0039142	Div ex
AU 9736885A	September 5, 1997	1997AU-0036885	N/A
EP 624164B1	November 16, 1993	1993WO-EP03217	N/A
EP 624164B1	November 16, 1993	1994EP-0901809	N/A
EP 624164B1	N/A	WO 9411394	Based on
DE 69316974E	November 16, 1993	1993DE-0616974	N/A
DE 69316974E	November 16, 1993	1993WO-EP03217	N/A
DE 69316974E	November 16, 1993	1994EP-0901809	N/A
DE 69316974E	N/A	EP 624164	Based on
DE 69316974E	N/A	WO 9411394	Based on
ES 2114170T3	November 16, 1993	1994EP-0901809	N/A
ES 2114170T3	N/A	EP 624164	Based on
SK 279227B6	November 16, 1993	1993WO-EP03217	N/A
SK 279227B6	November 16, 1993	1994SK-0000857	N/A
SK 279227B6	N/A	SK 9400857	Previous Publ.
JP 2812803B2	November 16, 1993	1993WO-EP03217	N/A
JP 2812803B2	November 16, 1993	1994JP-0511727	N/A
JP 2812803B2	N/A	JP 7507568	Previous Publ.
JP 2812803B2	N/A	WO 9411394	Based on
CZ 285155B6	November 16, 1993	1993WO-EP03217	N/A
CZ 285155B6	November 16, 1993	1994CZ-0001622	N/A
CZ 285155B6	N/A	CZ 9401622	Previous Publ.
CZ 285155B6	N/A	WO 9411394	Based on

JP 2812803 B2 INT-CL (IPC): A61K 9/08; A61K 9/20; A61K 37/02; A61K 38/00; A61K 38/04; A61K 38/08; A61K 38/10; A61K 38/12; C07K 7/06; C07K 7/08; C07K 7/64; C07K 14/435; C07K 14/47

RELATED-ACC-NO: 1993-387886

ABSTRACTED-PUB-NO: EP 624164B
BASIC-ABSTRACT:

A new class of biologically highly active peptides is characterised in that it comprises 8-15 amino acid residues, has the formula XaaZaaProProProXaaYaaProAlaAspZaaAlaXaaXaaXaa (I).

Where, Xaa = a neutral aliphatic amino acid residue like Ala, bAla, Leu, Ile, Gly, Val, Nle, Nva; Yaa = a basic amino acid residue like Lys, Arg, Orn, His; Zaa = an acidic amino acid residue like Glu, Asp, Aad or Apm; at least one of residues Xaa or Zaa can be omitted; the molecule may be cyclised by an amide bond between the first and last amino acid residue. The peptides can have 1-7 amino acids omitted.

USE - The peptides display biological activity equal to or greater than the parent protein BPC (Body Protecting Cpd., EP 432400). They can be used to protect organisms against stress and diseases by normalising the organic functions. They can be used to treat stress induced disturbances and illnesses, disturbances and lesions of liver and pancreas, atrophy of testes and sperm mobility, fertility disturbances, commercial breeding improvement, rickettsias illnesses, thyreoparathyreoidoctomy, diabetes mellitus, disturbances of adrenal gland, disturbances of the haemopoietic system, disturbances of coagulation, disturbances of bleeding, post-castration/menopausal disturbances, ischemic and toxic lesions, psychiatric disturbances, hypertension, disturbances of body temp., pain, tumours and depression (claimed).
ABSTRACTED-PUB-NO:

WO 9411394A
EQUIVALENT-ABSTRACTS:

A new class of biologically highly active peptides is characterised in that it comprises 8-15 amino acid residues, has the formula XaaZaaProProProXaaYaaProAlaAspZaaAlaXaaXaaXaa (I).

Where, Xaa = a neutral aliphatic amino acid residue like Ala, bAla, Leu, Ile, Gly, Val, Nle, Nva; Yaa = a basic amino acid residue like Lys, Arg, Orn, His; Zaa = an acidic amino acid residue like Glu, Asp, Aad or Apm; at least one of residues Xaa or Zaa can be omitted; the molecule may be cyclised by an amide bond between the first and last amino acid residue. The peptides can have 1-7 amino acids omitted.

USE - The peptides display biological activity equal to or greater than the parent protein BPC (Body Protecting Cpd., EP 432400). They can be used to protect organisms against stress and diseases by normalising the organic functions. They can be used to treat stress induced disturbances and illnesses, disturbances and lesions of liver and pancreas, atrophy of testes and sperm mobility, fertility disturbances, commercial breeding improvement, rickettsias illnesses, thyreoparathyreoidoctomy, diabetes mellitus, disturbances of adrenal gland, disturbances of the haemopoietic system, disturbances of coagulation, disturbances of bleeding, post-castration/menopausal disturbances, ischemic and toxic lesions, psychiatric disturbances, hypertension, disturbances of body temp., pain, tumours and depression (claimed).

CHOSEN-DRAWING: Dwg.0/7 Dwg.0/0

TITLE-TERMS: NEW PEPTIDE BASED BODY PROTECT COMPOUND PROTECT ORGANISM STRESS DISEASE NORMALISE ORGANIC FUNCTION

DERWENT-CLASS: B04 B05 C03

CPI-CODES: B04-C01B; C04-C01B; B04-C01C; C04-C01C; B04-N04B; C04-N04B;

B14-C01; C14-C01; B14-D01A; C14-D01A; B14-D01C; C14-D01C; B14-F02B; C14-F02B; B14-F02D; C14-F02D; B14-F04; C14-F04; B14-F08; C14-F08; B14-H01; C14-H01; B14-J01A; C14-J01A; B14-J01B3; C14-J01B3; B14-N12; C14-N12; B14-N13; C14-N13; B14-N17B; C14-N17B; B14-P02; C14-P02; B14-S04; C14-S04;

CHEMICAL-CODES:
Chemical Indexing M1 *01* Fragmentation Code F012 F014 F423 F521 H1 H100 H101 H102 H181 H182 J0 J011 J012 J1 J111 J171 J172 L250 M210 M211 M273 M280 M281 M311 M312 M314 M315 M320 M321 M332 M333 M340 M342 M343 M349 M371 M381 M391 M423 M510 M520 M521 M530 M540 M620 M710 M903 M904 P001 P220 P411 P422 P446 P448 P451 P520 P526 P528 P624 P625 P633 P721 P811 P813 P815 P816 V902 V912 V913 V921 V923 Markush Compounds 199422-42301-N 199422-42302-N

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C1994-083123

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Document Number 2

Entry 2 of 4 File: DWPI Nov 24, 1999

DERWENT-ACC-NO: 1998-481213
DERWENT-WEEK: 200001

TITLE: New isolated component of bromelain - used for e.g. treating cancers or immuno:deficiency(s) or as a vaccine adjuvant or anti-microbial agent

INVENTOR: ENGWERDA, C; MYNOTT, T L ; PEEK, K

PATENT-ASSIGNEE: ; CORTECS UK LTD[; CORTN]

PRIORITY-DATA:

1997GB-0006119	March 25, 1997
1997GB-0003827	February 25, 1997
1997GB-0003850	February 25, 1997
1997GB-0004252	February 28, 1997

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
ZA 9801577 A	November 24, 1999	N/A	070	C07K000/00
WO 9838319 A1	September 3, 1998	E	045	C12N015/57
AU 9863037 A	September 18, 1998	N/A	000	C12N015/57

DESIGNATED-STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-NO
ZA 9801577A	February 25, 1998	1998ZA-0001577	N/A
WO 9838319A1	February 25, 1998	1998WO-GB00591	N/A
AU 9863037A	February 25, 1998	1998AU-0063037	N/A
AU 9863037A	N/A	WO 9838319	Based on

INT-CL (IPC): A61K 38/48; A61K 39/39; C07H 0/00; C07K 0/00; C12N 9/50; C12N 15/57

RELATED-ACC-NO: 1998-481194;1998-481214

ABSTRACTED-PUB-NO: WO 9838319A
BASIC-ABSTRACT:

A fraction of an extract of bromelain plants which has a molecular weight of

approx. 27.45 kD as determined by SDS-PAGE and is obtainable by the following method:(a) dissolving bromelain in acetate buffer at pH 5.0; (b) separating the components of the bromelain by fast flow high performance liquid chromatography on ''S-Sepharose'' (RTM) eluting with a linear gradient of 0 to 0.8M NaCl in acetate buffer over 300ml; (c) collecting the fraction corresponding to the third peak off the column, appearing on the ascending edge of the first stem bromelain protease peak; and (d) isolating the protein from the fraction collected in (c). Also claimed are: (1) a protein which is a component of bromelain, has a molecular weight of approx. 27.45 kD as determined by SDS-PAGE, has an isoelectric point of 9.7 as determined by isoelectric focusing and has the amino terminal sequence: Val Leu Pro Asp Ser Ile Asp Trp Arg Gln Lys Gly Ala Val Thr Glu Val Lys Asn Arg Gly; (2) nucleic acid having a sequence which encodes a protein as in (1) or a complementary sequence.

USE - The bromelain fraction and protein act as immunostimulants and anti-cancer agents. They can be used for treating immunodeficiencies resulting from malnutrition, infection (e.g. HIV and malaria), tumours (e.g. lymphoid and myeloma), trauma (e.g. burns, wounds and surgery), medical treatment (e.g. with drugs such as steroids, cyclosporin and cyclophosphamide), protein loss (e.g. diarrhoea and burns), diabetes and old age (claimed). They can also be used as vaccine adjuvants and anti-microbial agents (claimed), e.g. for pathogens such as babesia, Brugia, Cryptosporidium, Encephalitoxoon, entamoeba, Leishmania, Naegleria, Onchocerca, Opisthorchis, Plasmodium, Schistosoma, Toxoplasma and Trypanosoma, Bacillus, Brucella, Burkholderia, Clostridium, Ehlichia, Francisella, Klebsiella, Legionella, Listeria, Micrococcus, Pseudomonas Rickettsia, Salmonella, Staphylococcus, Yersinia, Chlamydia especially C. trachomatis, as M. avium, M. leprae, M. tuberculosis, Aspergillus, Candida, Cryptococcus, Histoplasma, Pneumocystis, Saccharomyces, Coxsackievirus, Ectomelia virus, encephalomyocarditis virus, Epstein-Barr virus, Herpes simplex virus, HIV type 1, Japanese encephalitis virus, mouse hepatitis virus, paravirus, poliovirus, rabies virus, simian virus 40, vaccinia virus and vesicular stomatitus virus. They can also be used for treating cancers (claimed).

CHOSEN-DRAWING: Dwg.0/9

TITLE-TERMS: NEW ISOLATE COMPONENT BROMELAIN TREAT CANCER IMMUNO DEFICIENT VACCINE ADJUVANT ANTI MICROBE AGENT

DERWENT-CLASS: B04 C03 D16

CPI-CODES: B04-C01; C04-C01; B04-L05C; C04-L05C; B14-H01; C14-H01; D05-C02; D05-H07; D05-H12A; D05-H17A;

CHEMICAL-CODES:
Chemical Indexing M1 *01* Fragmentation Code M421 M423 M431 M710 M782 M903 N161 N164 P210 P220 P616 P633 P735 P942 Q233 V270 V279 V280 V288 V752 V753 V818 Chemical Indexing M2 *02* Fragmentation Code B615 B701 B711 B720 B732 B815 B831 B840 F012 F018 F640 H6 H602 H608 H681 H689 M280 M312 M322 M332 M342 M362 M392 M411 M431 M510 M521 M530 M540 M782 M903 M904 M910 N161 N164 P210 P220 P616 P633 P735 P942 Q233 V270 V279 V280 V288 V818 Ring Index 07746 Specfic Compounds 00008K 00008M 00008T Registry Numbers 0008U Chemical Indexing M1 *03* Fragmentation Code H1 H100 H102 H181 H4 H401 H481 H8 J0 J011 J1 J171 M210 M211 M273 M280 M281 M311 M313 M314 M315 M321 M333 M340 M342 M343 M349 M381 M391 M421 M423 M431 M510 M520 M530 M540 M620 M782 M903 M904 N161 N164 P210 P220 P616 P633 P735 P942 Q233 V030 V270 V279 V280 V288 V818 V901 V913 V923 Specfic Compounds 04466K 04466M Chemical Indexing M1 *04* Fragmentation Code H1 H100 H102 H181 H4 H401 H481 H7 H721 H8 J0 J011 J1 J171 M210 M212 M273 M280 M281 M311 M313 M314 M315 M321 M333 M340 M342 M343 M349 M381 M391 M421 M423 M431 M510 M520 M530 M540 M620 M782 M903 M904 N161 N164 P210 P220 P616 P633 P735 P942 Q233 V030 V270 V279 V280 V288 V818 V901 V913 V923 V925 Specfic Compounds 04467K 04467M Chemical Indexing M1 *05* Fragmentation Code H1 H100 H102 H181 H4 H401 H481 H7 H721 H8 J0 J011 J1 J171 M210 M211 M212 M273 M280 M281 M311 M313 M314 M315 M321 M333 M340 M342 M343 M349 M381 M391 M421 M423 M431 M510 M520 M530 M540 M620 M782 M903 M904 N161 N164 P210 P220 P616 P633 P735 P942 Q233 V030 V270 V279 V280 V288 V818 V901 V913 V923 V925 Specfic Compounds 04468K 04468M Chemical Indexing M1 *06*

Fragmentation Code H1 H100 H102 H181 H4 H401 H481 H7 H721 H8 J0 J011 J1 J171
M210 M211 M212 M273 M280 M281 M311 M313 M314 M315 M321 M333 M340 M342 M343
M349 M381 M391 M421 M423 M431 M510 M520 M530 M540 M620 M782 M903 M904 N161
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V913 V923 V925 Specfic Compounds 04469K 04469M Chemical Indexing M1 *07*
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N164 P210 P220 P616 P633 P735 P942 Q233 V030 V270 V279 V280 V288 V818 V901
V913 V923 V925 Specfic Compounds 17044K 17044M

UNLINKED-DERWENT-REGISTRY-NUMBERS: 0195U

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C1998-145718

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Database: Derwent World Patents Index

Refine Search: (coxiella or burnetii) same (bcg or tb or tuberculosis)

Search History

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DWPI	(coxiella or burnetii) same (bcg or tb or tuberculosis)	2	L6
DWPI	(coxiella or burnetii or rickettsia) same bcg	1	L5
DWPI	(coxiella or burnetii or rickettsia) same (diabetes or IDDM) same bcg	0	L4
DWPI	(coxiella or burnetii or rickettsia) same (diabetes or IDDM) same hsp	0	L3
DWPI	(coxiella or burnetii or rickettsia) and (diabetes or IDDM)	4	L2
DWPI	(coxiella or burnetii) and (diabetes or IDDM)	1	L1

1 : *Proc Natl Acad Sci U S A* 1999 Apr 27;96(9):5159-63

The 60-kDa heat shock protein modulates allograft rejection.

Birk OS, Gur SL, Elias D, Margalit R, Mor F, Carmi P, Bockova J, Altmann DM, Cohen IR

Department of Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel.

Allograft rejection is a process of immune reactivity triggered by foreign transplantation antigens. We now demonstrate that the 60-kDa heat shock protein (hsp60), a molecule that is identical in the donor and the recipient, can regulate allograft immunity. In wild-type mice, hsp60 expression was greatly enhanced in allografts being rejected. By using MHC class II (Ealpha) promoter hsp60 transgenic mice either as donors of skin with enhanced expression of hsp60, or as allograft recipients with decreased hsp60 autoimmunity, we found that augmented expression of mouse hsp60 in the allograft accelerated its rejection, whereas reduced autoimmunity to mouse hsp60 in graft recipients delayed the process. Moreover, in nontransgenic mice, therapeutic administration of hsp60 or hsp60 peptides, known to modulate naturally occurring hsp60 autoimmunity, led to delayed allograft rejection. Thus, we demonstrate that hsp60 expression and hsp60 autoimmunity can influence and modify the immune response to foreign antigens. Hence, autoimmunity to self-hsp60 epitopes is not necessarily an aberration, but may serve physiologically and therapeutically to modulate foreign immunity.

PMID: 10220435, UI: 99238499

1 : *J Autoimmun* 1999 Mar;12(2):121-9 Related Articles, Books, LinkOut

T cell proliferative responses of type 1 diabetes patients and healthy individuals to human hsp60 and its peptides.

Abulafia-Lapid R, Elias D, Raz I, Keren-Zur Y, Atlan H, Cohen IR

Department of Immunology, The Weizmann Institute of Science, Rehovot, Israel.

T cell responses to peptide epitopes of the 60 kDa heat shock protein (hsp60) have been shown to play a role in the pathogenesis of type 1 insulin-dependent diabetes mellitus (IDDM) in mice. To test whether hsp60 autoimmunity might be involved in human type 1 diabetes, we studied T cell proliferative responses (stimulation index; SI) to intact human hsp60, to hsp60 peptides and to a recall antigen (tetanus toxoid) in 25 newly diagnosed type 1 diabetes patients, in 22 type 2 (non-insulin-dependent diabetes mellitus, NIDDM) patients, and in 25 healthy blood donors. There were no significant differences between the T cell responses of the three groups to tetanus toxoid. However, the responses to hsp60 of the type 1 diabetes group (median SI=5) were significantly greater (P<0. 01) than those of the type 2 group (median SI=1.67) and of the blood donors (median SI=1.7). Epitope mapping revealed significant responses to at least seven different peptides, with prevalent responses to the p277 peptide previously mapped in NOD mice and to peptide p32. Thus, newly diagnosed type 1 diabetes patients, similar to prediabetic and newly diabetic NOD mice, show heightened autoimmunity to hsp60 and hsp60 peptides. Copyright 1999 Academic Press.

PMID: 10047432, UI: 99158649

Treatment of NOD diabetes with a novel peptide of the hsp60 molecule induces Th2-type antibodies.

Bockova J, Elias D, Cohen IR

Department of Immunology, The Weizmann Institute of Science, Rehovot, 76100, Israel.

A peptide from the sequence of hsp60 molecule, designated p277, has been shown to be functionally involved in modulating the development of auto-immune diabetes in the NOD mouse: administration of p277 to NOD mice can arrest the diabetogenic autoimmune process, even when far advanced. Is p277 the only hsp60 peptide able to modulate the disease? We mapped T cell responses to peptides spanning the mouse hsp60 molecule and identified an immunogenic peptide, designated p12, that is also functional in arresting NOD diabetes. Although no spontaneous T cell reactivity to p12 could be detected in NOD mice, subcutaneous administration of 100 &mgr;g of p12 in mineral oil to 10-week-old female NOD mice, similar to treatment with p277, significantly prevented progression of the disease. Administration of other immunogenic peptides was not effective. A peptide from the glutamic acid decarboxylase (GAD65) sequence, GADp35, and a peptide from the myco-bacterial hsp60 molecule did not influence the development of diabetes. The effectiveness of hsp60 peptides p12 and p277 was associated with the induction of antibodies to the peptides of the IgG1 and IgG2b isotypes, antibodies which appear to be regulated by anti-inflammatory cytokines. There was a negative correlation between the amounts of antibodies induced by the hsp60 peptides and the level of blood glucose. Thus, more than one peptide of the hsp60 molecule can be used to inhibit the development of NOD diabetes, and the effect of peptide therapy appears to be associated with the induction of specific antibody isotypes.

PMID: 9237795, UI: 97383171

1 : *J Autoimmun* 2000 Mar;14(2):133-42 Related Articles, Books, LinkOut

Prevention of diabetes in the NOD mouse by a Th1 clone specific for a hsp60 peptide.

Feili-Hariri M, Frantz MO, Morel PA

Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA.

Peptide-based therapies have been shown to be effective in the prevention of diabetes in the NOD mouse. We have been interested in the T cell response elicited by such therapies and have been studying a T cell clone (C3.5) specific for hsp60 AA 437-460, generated following immunization with the hsp60 437-460 peptide. The C3.5 clone was CD4(+), Vbeta8.3 TCR(+), I-A(g7)restricted and of the Th1 type. The injection of this clone into prediabetic NOD mice prevented the adoptive transfer of the disease and suppressed the development of spontaneous diabetes. This effect was reflected in a reduction in the degree and severity of insulitis in mice injected with this clone. In addition, an antibody response was elicited to the C3.5 clone in mice given multiple injections of the clone. The epitope recognized by C3.5 is located in the N-terminus of the hsp60 AA 437-460 peptide, and this clone was unable to recognize the native hsp60 molecule. These data raise questions concerning the mechanism by which peptide-based therapies prevent autoimmune disease. Copyright 2000 Academic Press.

PMID: 10677244, UI: 20143511

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Related Resources

1 : *Clin Immunol Immunopathol* 1997 Aug;84(2):103-6

Related Articles, Books, LinkOut

The Th1/Th2 dichotomy, hsp60 autoimmunity, and type I diabetes.

Cohen IR

Department of Immunology, Weismann Institute of Science, Rehovot, Israel.

This paper presents some questions and issues regarding the concept of the Th1/Th2 dichotomy and summarizes results using an hsp60 peptide to treat the spontaneous autoimmune process of diabetes in NOD mice.

Publication Types:
- Review
- Review, tutorial

PMID: 9245539, UI: 97401050

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1 : *Proc Natl Acad Sci U S A* 1991 Apr 15;88(8):3088-91

Vaccination against autoimmune mouse diabetes with a T-cell epitope of the human 65-kDa heat shock protein.

Elias D, Reshef T, Birk OS, van der Zee R, Walker MD, Cohen IR

Department of Cell Biology, Weizmann Institute of Science, Rehovot, Israel.

Insulin-dependent diabetes mellitus is caused by autoimmune destruction of the insulin-producing beta cells resident in the pancreatic islets. We recently discovered that the pathogenesis of diabetes in NOD strain mice was associated with T-cell reactivity to an antigen cross-reactive with a mycobacterial 65-kDa heat shock protein. To identify peptide epitopes critical to the insulin-dependent diabetes mellitus of NOD mice, we studied the specificities of helper T-cell clones capable of causing hyperglycemia and diabetes. We now report the identification of a functionally important peptide within the sequence of the human variant of the 65-kDa heat shock protein molecule. T-cell clones recognizing this peptide mediate insulitis and hyperglycemia. Alternatively, the T cells can be attenuated and used as therapeutic T-cell vaccines to abort the diabetogenic process. Moreover, administration of the peptide itself to NOD mice can also down-regulate immunity to the 65-kDa heat shock protein and prevent the development of diabetes. Thus, T-cell vaccination and specific peptide therapy are feasible in spontaneous autoimmune diabetes.

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1 : *Proc Natl Acad Sci U S A* 1990 Feb;87(4):1576-80

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Induction and therapy of autoimmune diabetes in the non-obese diabetic (NOD/Lt) mouse by a 65-kDa heat shock protein.

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Insulin-dependent diabetes mellitus is caused by autoimmune destruction of the insulin-producing beta cells of the pancreas. The results described here indicate that a beta-cell target antigen in non-obese diabetic (NOD/Lt) mice is a molecule cross-reactive with the 65-kDa heat shock protein (hsp65) of Mycobacterium tuberculosis. The onset of beta-cell destruction is associated with the spontaneous development of anti-hsp65 T lymphocytes. Subsequently hsp65 cross-reactive antigen becomes detectable in the sera of the prediabetic mice and some weeks later anti-hsp65 antibodies, anti-insulin antibodies, and anti-idiotypic antibodies to insulin antibodies become detectable. The hsp65-cross-reactive antigen, the autoantibodies, and the T-cell reactivity then decline with the development of overt insulin-dependent diabetes. The importance of hsp65 in the pathogenesis of insulin-dependent diabetes was confirmed by the ability of clones of anti-hsp65 T cells to cause insulitis and hyperglycemia in young NOD/Lt mice. Moreover, hsp65 antigen could be used either to induce diabetes or to vaccinate against diabetes, depending on the form of its administration to prediabetic NOD/Lt mice. Other antigens such as the 70-kDa heat shock protein (hsp70) had no effect on the development of diabetes.

PMID: 2406723, UI: 90160369

Autoimmune diabetes induced by the beta-cell toxin STZ. Immunity to the 60-kDa heat shock protein and to insulin.

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Administered at a suitably low dose, the toxin streptozotocin (STZ) can trigger an autoimmune process leading to destruction of the beta-cells of the pancreatic islets. In this study, we examined specific immunological reactions in mice before and during the development of STZ-induced autoimmune diabetes. We now report that the development of spontaneous autoantibodies to insulin can serve as a marker of susceptibility to a low dose of STZ. Susceptible male mice of the C57BL/KsJ strain manifested such anti-insulin antibodies, and resistant female mice did not. Administration of a low dose of STZ (five daily doses each of 30 mg/kg) induced transient hyperglycemia approximately 20-30 days later, which temporarily remitted but was followed by intractable diabetes approximately 2.5 months later. The diabetogenic process triggered by the low dose of STZ was associated with an increase in the level of anti-insulin antibodies bearing the Dana and Micha (DM) idiotype, later followed by the appearance of anti-idiotypic antibodies that peaked before the onset of diabetes. Antibodies and T-cells reactive to hsp60 (heat shock protein) were triggered by the low-dose STZ administration and persisted throughout the period that preceded clinical diabetes. T-cells reactive to the p277 peptide of hsp60 were also observed. Finally, active immunization to hsp60 caused transient hyperglycemia by itself and also aggravated the hyperglycemia induced by low-dose STZ. Thus, autoantibodies to insulin can indicate susceptibility to a toxic trigger of diabetes, and a low dose of a toxin can activate the insulin and hsp60 autoimmunity that has been detected previously in the spontaneous autoimmune diabetes of NOD strain mice.

PMID: 8039607, UI: 94314108

Heat shock proteins in autoimmune disease. From causative antigen to specific therapy?

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Heat shock proteins (hsp) are highly conserved from bacteria to man. Bacterial hsp, with approximate molecular weights of 60 kDa (hsp60), are immunodominant antigens that are immunologically cross-reactive with their mammalian counterparts. Hsp molecules are therefore useful in studies of fundamental questions concerning immune responses to foreign as opposed to self antigens. The finding that immune responses to hsp are associated with both experimentally-induced and spontaneous autoimmune diseases in animals has prompted intensive research to assess the role of bacterial hsp as the etiological agents involved in the development of autoimmune diseases. Recent evidence from animal models of autoimmune disease has clearly demonstrated the involvement of hsp in both the pathogenesis and the immunoregulation of autoimmune diseases. Studies with arthritogenic and diabetogenic T cell clones have identified immunogenic epitopes of hsp. These have been shown to ameliorate adjuvant arthritis in Lewis rats, and insulin-dependent diabetes mellitus (IDDM) in non-obese diabetic (NOD) mice. Such studies may have important therapeutic implications for the future treatment of human autoimmune disease.

Publication Types:

- Review
- Review literature

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Induction of diabetes in standard mice by immunization with the p277 peptide of a 60-kDa heat shock protein.

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We previously reported that immunity to the p277 peptide of the human 60-kDa heat shock protein (hsp60) was a causal factor in the diabetes of non-obese diabetic (NOD) mice, which are genetically prone to develop spontaneous autoimmune diabetes. The present study was done to test whether immunization with the p277 peptide could cause diabetes in standard strains of mice. We now report that a single administration of the p277 peptide conjugated to carrier molecules such as bovine serum albumin or ovalbumin can induce diabetes in C57BL/6 mice and in other strains not genetically prone to develop diabetes. The diabetes was marked by hyperglycemia, insulitis, insulin autoantibodies, glucose intolerance and low blood levels of insulin. The diabetes could be transferred to naive recipients by anti-p277 T cell lines. Similar to other experimentally induced autoimmune diseases, the autoimmune diabetes remitted spontaneously. After recovery, the mice were found to have acquired resistance to a second induction of diabetes. Susceptibility to induced diabetes in C57BL/6 mice was influenced by sex (males were much more susceptible than were females) and by class II genes in the major histocompatibility complex (B6.H-2bm12 mice with a mutation in the MHC-II molecule were relatively resistant). Other strains of mice susceptible to induced diabetes were C57BL/KSJ, C3HeB/FeJ, and NON/Lt. BALB/c and C3H/HeJ strains were relatively resistant. Immunization to p277-carrier conjugates could also induce transient hyperglycemia in young NOD mice, but upon recovery from the induced diabetes, the NOD mice were found to have acquired resistance to later development of spontaneous diabetes. Thus, T cell immunity to the p277 peptide can suffice to induce diabetes in standard mice, and a short bout of induced diabetes can affect the chronic process that would otherwise lead to spontaneous diabetes in diabetes-prone NOD mice.

PMID: 7589082, UI: 96062035

1 : *Diabetes* 1995 Sep;44(9):1132-8 Related Articles, Books, LinkOut

Treatment of autoimmune diabetes and insulitis in NOD mice with heat shock protein 60 peptide p277.

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We recently showed that a peptide of the M(r) 60,000 heat shock protein molecule, designated peptide p277, is a target of T-cells in autoimmune diabetes in NOD mice. Indeed, the p277 peptide could be used as a therapeutic agent to arrest the autoimmune process even after it was far advanced. The present study was done to document the effects of p277 therapy on inflammation of the islets and on T-cell responsiveness to p277. Groups of female NOD mice of various ages up to 17 weeks were treated with a single inoculation of p277 given before or after the onset of overt hyperglycemia. We now report that fragments of p277 can affect diabetes but that optimal therapy requires the whole peptide. The positive response to p277 was dependent on administration of a threshold dose of peptide. Therapy was accompanied by the regression of intra-islet inflammation and the reappearance of histologically normal islets. Successful peptide therapy was associated with downregulation of T-cell immunity to p277. Adoptive transfer experiments demonstrated that the spleen cells of p277-treated mice were no longer diabetogenic and also could suppress the diabetogenic potential of cotransferred spleen cells of untreated female NOD mice. These results indicate that specific treatment of diabetes with a defined peptide can reprogram the autoimmune response.

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